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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/787,916	07/09/2001	Hiroshi Shiku	P20854	1184

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GREENBLUM & BERNSTEIN, P.L.C.
1950 ROLAND CLARKE PLACE
RESTON, VA 20191

EXAMINER
EWOLDT, GERALD R

ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
07/09/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

gbpatent@gbpatent.com
pto@gbpatent.com

Office Action Summary	Application No.	Applicant(s)	
	09/787,916	SHIKU ET AL.	
	Examiner	Art Unit	
	G. R. Ewoldt, Ph.D.	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 June 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13,14,28 and 30-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13,14,28 and 30-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment and remarks filed 5/04/07 are acknowledged.

2. Claims 13, 14, 28, and 30-37 are pending and being acted upon.

3. In view of Applicant's amendment, the previous rejection of Claim 27 under 35 U.S.C. 112, first paragraph for the introduction of new matter into the claims has been withdrawn.

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 13, 14, 28, and 30-36 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Nestle et al. (1998, IDS) in view of Gu et al. (1997, IDS).

As set forth previously, Nestle et al. teaches a method for inducing cellular immunity comprising isolating a DC APC, reacting said APC with a tumor antigen, and returning the resulting cell to the living body by parenteral administration (see particularly Methods, page 331, column 2 - page 332, column 1).

The reference differs from the claimed invention only in that it does not teach an APC loaded with the ErbB-2 antigen by reacting with a complex comprising a hydrophobized polysaccharide comprising mannan or a polysaccharide comprising the limitations of Claim 4 wherein the sterol is cholesterol.

Gu et al. teaches that a cholesterol bearing mannan polysaccharide complexed to an ErbB-2 antigen (an antigen overexpressed in a wide range of human adenocarcinomas, see Abstract) can be used to induce CD8+ CTLs (page 19, column 2, second full paragraph and page 23, column 1) by a mechanism of facilitating the entry of the antigen into the MHC Class I pathway for presentation by APCs (see particularly page 24, column 1, first full paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to produce a product for, and perform a method for, inducing cellular immunity comprising isolating a DC APC, reacting said APC with a tumor antigen, and returning the resulting cell to the living body by parenteral administration, as taught by Nestle et al. One of ordinary skill in

the art at the time of the invention would have been motivated to employ the cholesterol bearing mannan polysaccharide complexed to an ErbB-2 antigen of Gu et al. given the teachings of the reference that the ErbB-2 antigen is overexpressed in a wide range of human adenocarcinomas (and would thus provide an obvious target for immunotherapy) and that the use of the cholesterol bearing mannan polysaccharide facilitates the entry of the antigen into the MHC Class I pathway for presentation by APCs.

Applicant's arguments, filed 5/04/07, have been fully considered but they are not persuasive. Applicant argues that Nestle et al. teaches away from employing a single peptide as taught by Gu et al.

A careful reading of Gu et al. reveals that ErbB-2 is just one of many cancer antigens that might be employed in a method of inducing cellular immunity. See, for example, the Introduction wherein the reference teaches that multiple antigen peptides recognized by CTLs have been identified. See also the Discussion wherein the reference again teaches that multiple cancer antigen peptides have been identified and that vaccines might utilize, "antigen peptides or recombinant proteins containing antigen peptide sequences". Again, note the plural of antigens and sequences. Clearly then, the authors are teaching the induction of cellular immunity to erbB-2 as an exemplary embodiment and not as a limitation.

Applicant again asserts unexpected results.

The asserted unexpected results have been addressed previously. Again, an argument of unexpected results employed post-filing in an attempt to overcome an art rejection has not been found to be persuasive.

6. Claims 13, 14, 28, and 30-36 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Nestle et al. (1998, IDS) in view of Gu et al. (1998, of record).

As set forth previously, Nestle et al. has been discussed above.

The reference differs from the claimed invention only in that it does not teach an APC loaded with antigen (ErbB2 also known as HER2) by reacting with a complex comprising a hydrophobized polysaccharide comprising mannan or pullulan, or a polysaccharide comprising the limitations of Claim 4 wherein the sterol is cholesterol.

Gu et al. teaches that a cholesterol bearing mannan or pullulan polysaccharide complexed to a HER2 antigen (see Materials and Methods) can be used to induce CD8+ cellular immunity (see particularly Figures 1 and 4), while antigen alone is ineffective, by a mechanism of facilitating the entry of the antigen into

an APC through a carbohydrate-recognizing receptor such as DEC-205, and entry into the cytosol (for transport to MHC Class I) after phagocytosis (see particularly page 3389, column 2-3390).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to produce a product for, and perform a method for, inducing cellular immunity comprising isolating a DC APC, reacting said APC with a tumor antigen, and returning the resulting cell to the living body by parenteral administration, as taught by Nestle et al. One of ordinary skill in the art at the time of the invention would have been motivated to employ the cholesterol bearing mannan or pullulan polysaccharide complexed to a HER2 antigen of Gu et al. given the teachings of the reference that hydrophobized polysaccharide-antigen complex facilitates the entry of the antigen into an APC through a carbohydrate-recognizing receptor such as DEC-205, and entry into the cytosol (for transport to MHC Class I) after phagocytosis, for superior antigen presentation and cellular immunity.

Applicant's arguments, filed 5/04/07, have been fully considered but they are not persuasive. Applicant again argues that Nestle et al. teaches away from employing a single peptide as taught by Gu et al.

Again, it is clear that Gu et al. envision more than the employment of single peptides in cancer vaccines. Again, in the Introduction, the reference teaches that multiple cancer rejection antigens are known. Further, in the Discussion, the reference teaches that vaccines employing multiple epitopes (whole proteins that would be processed into multiple different peptides) may be more efficacious than vaccines employing single peptides. Thus, it is clear that the authors are teaching the induction of cellular immunity to a single peptide antigen as an exemplary embodiment and not as a limitation.

Applicant again asserts unexpected results.

The asserted unexpected results have been addressed previously. Again, an argument of unexpected results employed post-filing in an attempt to overcome an art rejection has not been found to be persuasive.

7. Claims 13, 14, 28, and 30-36 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Kohno et al. (1996, of record) in view of Gu et al. (1997, of record), Nagarkatti et al (1990), and Terao et al. (1995).

As set forth previously, Kohno et al. teaches the *in vitro* stimulation of Th1 CD4+ T cells, including increased production of IFN-γ, by DC APC capable of inducing cellular immunity, said cell having been produced by

reacting *in vitro* with the hydrophobized polysaccharide pullulan and an antigen (see particularly page 213, column 1 and Figure 2).

The reference differs from the claimed invention only in that it does not teach a method of inducing cellular immunity *in vivo* nor the use of the ErbB-2 antigen.

Gu et al. (1997) teaches that ErbB-2 is overexpressed in a wide range of adenocarcinomas (see particularly the Abstract).

Nagarkatti et al. (1990) teaches that Th1 CD4+ T cells can mediate tumor rejection (see particularly, Table V).

Terao et al. (1995) teaches that Th1 CD4+ T cells expressing IFN-γ can be used in anti-tumor immunotherapy, particularly against poorly immunogenic tumors (see particularly page 146, The anti-tumor activity of MH2 against three tumor cell lines, and page 150, column 2).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to induce cellular immunity by the *in vitro* stimulation of Th1 CD4+ T cells, including increased production of IFN-γ, by DC APC capable of inducing cellular immunity, said cell having been produced by reacting *in vitro* with the hydrophobized polysaccharide pullulan and an antigen, as taught by Kohno et al., employing the ErbB-2 antigen which is overexpressed in a wide range of adenocarcinomas, as taught by Gu et al. The ordinarily skilled artisan would have been motivated to employ the Th1 cells produced by the claimed method in immunotherapy, i.e., administering to a patient to induce cellular immunity, given the teachings of Nagarkatti et al., that Th1 CD4+ T cells can mediate tumor rejection, and Terao et al. that Th1 CD4+ T cells expressing IFN-γ can be used in effective anti-tumor immunotherapy, particularly against poorly immunogenic tumors.

Applicant's arguments, filed 5/04/07, have been fully considered but they are not persuasive. Applicant argues that Kohno et al. does not disclose a hydrophobized polysaccharide and an antigen.

In Kohno et al., SBP is the antigen complexed to pullulan, the hydrophobized polysaccharide. Looking to the specification for the definition of a "hydrophobized polysaccharide", at page 6 it is disclosed that, "According to the present invention, the hydrophobized polysaccharides are prepared by introducing hydrophobic groups into the aforementioned polysaccharides". Thus, this broad definition encompasses *any* polysaccharide comprising *any* hydrophobic groups. Clearly, both SBP and pullulan comprise at least some "hydrophobic groups", including the newly added "alkyl group" or "sterol residue", thus the conjugate of the reference is the conjugate of the instant claims.

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claim 37 stands rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. This is a new matter rejection.

The specification and the claims as originally filed do not provide support for the invention as now claimed, specifically:

As set forth previously, B) The method … wherein the antigen consists of a polypeptide consisting of residues 1-147 of ErbB-2 fused to a histidine hexamer at the N-terminal.

Regarding B), Example 1 disclose only a specific composition comprising a specific hydrophobized polysaccharide combination (a cholesterol-modified mannan and pullulan), i.e., not the generic hydrophobized polysaccharide of the claim. Further, the Example discloses only a polypeptide consisting of human ErbB-2 and not the generic ErbB-2 employed in the claim, and then this polypeptide is not disclosed as used in the generic method of inducing cellular immunity. The complex of the Example is employed only *in vivo* employing BALB/c mice or *in vitro* employing human peripheral blood monocytes.

Applicant's arguments, filed 5/04/07, have been fully considered but they are not persuasive. Applicant argues that the amendment to the claim has overcome the rejection.

Applicant's amendment has only overcome the human erbB-2 aspect of the rejection. As set forth in the rejection, the claim still recites the use of a human erbB-2 fragment in a generic context which the example does not disclose.

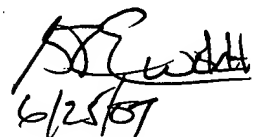
10. No claim is allowed.

11. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (571) 272-0843. The examiner can normally be reached Monday through Thursday from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

13. **Please Note**: Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197.


6/25/07

G.R. Ewoldt, Ph.D.
Primary Examiner
Technology Center 1600